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Abstract

Background: Long-term exposure to traffic-related air pollution may increase blood pressure (BP) and induce hypertension; however evidence is limited and this association may be confounded by traffic noise, and biased due to inappropriate control for BP-lowering medications.

Objectives: We evaluated the association between long-term traffic-related air pollution, BP and prevalent hypertension, adjusting for transportation noise, and assessing different methodologies to control for BP-lowering medications.

Methods: We measured systolic (SBP) and diastolic BP (DBP) at baseline (years 2003-2005) in 3700 participants, aged 35-83, from a population-based cohort in Spain. We estimated home outdoor annual average concentrations of nitrogen dioxide (NO_2) with a land-use regression model. We used multivariate linear and logistic regression.

Results: A 10-$\mu g/m^3$ increase in NO_2 levels was associated with 1.34 mmHg (95% CI: 0.14, 2.55) higher SBP in non-medicated individuals, after adjusting for transportation noise. Results were similar in the entire population after adjusting for medication, as commonly done, but weaker when other methods were used to account for medication use. For example, when 10 mmHg were added to the measured SBP levels of medicated participants, the association was β = 0.78 (95% CI: -0.43, 2.00). NO_2 was not associated with hypertension. Associations of NO_2 with SBP and DBP were stronger in participants with cardiovascular disease, and the association with SBP was stronger in those exposed to high traffic density and traffic noise levels $\geq$ 55dB(A).

Conclusions: We observed a positive association between long-term exposure to NO_2 and SBP, after adjustment for transportation noise, which was sensitive to the methodology used to account for medication.

Introduction

Air pollution may not only trigger cardiovascular events but promote chronic pathologies and subsequent cardiovascular disease (CVD) (Pope and Dockery 2006), which would further contribute to cardiovascular mortality (Brook et al. 2010). This is supported by animal studies (Brook et al. 2010) and associations between long-term exposure to air pollutants and markers of atherosclerosis (Künzli et al. 2011). Long-term exposure to air pollution may also contribute to CVD through high blood pressure (BP), an established determinant of atherogenesis and CVD, and a leading cause of death (Lopez et al. 2006). Given the ubiquity of air pollution, identifying the association with high BP is of high relevance for public health.

There is increasing evidence that short-term exposure to air pollution (i.e. hours to months) is positively associated with systolic BP (SBP) and/or diastolic BP (DBP) levels, although there exists some heterogeneity in previous studies (Brook et al. 2010, 2011; Chuang et al. 2010; Delfino et al. 2010). Less is known about long-term exposure. Four cross-sectional studies reported significant positive associations of annual average home outdoor concentrations of different pollutants with BP in population-based samples, the elderly, or men (Chuang et al. 2011; Dong et al. 2013; Fuks et al. 2011; Schwartz et al. 2012). In contrast, another cross-sectional study reported inverse associations with SBP in a population-based sample (Sørensen et al. 2012). Regarding the prevalence and incidence of hypertension, the few studies available provide inconsistent evidence (Coogan et al. 2012; Dong et al. 2013; Fuks et al. 2011; Johnson and Parker 2009; Sørensen et al. 2012). Plausible biological pathways involve autonomic nervous system imbalance, oxidative stress and systemic inflammation, and subsequent endothelial dysfunction (Brook et al. 2009; Mills et al. 2008).

Several studies suggest that near-road traffic-related air pollution – indicated by residential proximity to traffic – could be particularly important for CVD (e.g. Brook et al. 2009; Hoffmann et al. 2007; Künzli et al. 2010). Traffic-related air pollution could also be relevant for BP (Schwartz et al. 2012). Traffic is also a main source of noise, which has been associated with hypertension in the long-term (van Kempen and Babisch 2012), and may potentially confound or modify the effects of air pollution on BP. However, few studies have adjusted for it (Fuks et al. 2011; Sørensen et al. 2012).

A particular challenge and weakness of previous publications relates to dealing with BP-lowering medication. Conceptually, air pollution would lead to high BP, and subsequently to treatment, which would decrease BP levels. Thus, treatment would be a mediator, not a confounder, of the measured BP levels in those taking BP-lowering medication. Therefore, the common procedure of adjusting for medication may introduce bias, as previously suggested (Fuks et al. 2011; Schwartz et al. 2012; Tobin et al. 2005).

The purpose of this cross-sectional study was to evaluate the association of home outdoor estimates of annual average concentrations of NO_2, a marker of traffic-related air pollution, with SBP, DBP, and the prevalence of hypertension, adjusting for traffic-related noise, and particularly evaluating different procedures to account for BP-lowering medication. Furthermore, we investigated whether residential proximity to main roads, high traffic noise levels, and different population characteristics modified the association between pollution and BP. We capitalize on the large and well-defined adult population of the REGICOR cohort studies conducted in Girona (Spain).

Methods

Study population

The study population consisted of 3,836 individuals, aged 35–83 who participated at baseline (years 2003 to 2006) in one of the population-based cohorts of the REGICOR project, described elsewhere (Grau et al. 2007). Briefly, we randomly selected potential participants from all non-institutionalized inhabitants of the city of Girona. From those, a 73.8% attended the baseline visit. Girona is a typical mid-sized Mediterranean urban area of nearly 100,000 inhabitants in the north-east of Spain with a densely populated centre where traffic is expected to be the main contributor to air pollution levels. The study was approved by Hospital del Mar Research Institute ethics committee and participants signed written informed consent.

Outcomes and health assessment

Participants fasted for 10 h previous to examination. Trained nurses performed the examinations from 8 to 11 am. BP was measured at the beginning, following the Joint National Committee (JNC) VII recommendations (Chobanian et al. 2003), in sitting position, and with a calibrated automatic device (OMRON 711) that also registered heart rate. The first and second measurements were done after at least 10 and 3 minutes of rest, respectively. If measurements differed by 5 mmHg or more, a third measurement was taken. To avoid white coat effect, we used the last measurement available. The nurses also withdrew blood to obtain cholesterol, triglyceride and fasting glucose levels.

We collected individual questionnaire information on smoking, weekly leisure time physical activity (based on Minnesota's questionnaire) (Elosua et al. 2000), daily alcohol intake, living alone, family history of cardiovascular deaths, diet (defined with the REGICOR score for

adherence to Mediterranean diet) (Schröder et al. 2004), educational level, and occupational status. In addition, we assessed socio-economical status (SES) with the deprivation index at the census tract level (Domínguez-Berjón and Borrell 2005). We defined diabetes as fasting blood glucose level ≥ 126 mg/dl or reported treatment with antidiabetic drugs, body mass index (BMI) as weight/height^2 (kg/m^2), and cardiovascular disease as having ever had a cardiovascular event (myocardial infarction or stroke) or cardiovascular-related surgery intervention.

We defined hypertension as having SBP or DBP ≥ 140/90 mmHg (Chobanian et al. 2003), respectively, or as taking antihypertensive treatment, reported with a positive response to the question "Do you take or have you taken any doctor-prescribed medication to reduce blood pressure in the last two weeks?". For BP analysis, we accounted for any "BP-lowering medication". It included antihypertensive treatment, as defined with the question above, or the use of any treatment from the medication list provided by participants and coded by a physician as "antihypertensive" or "beta-blocker" (i.e. diuretics, ACE inhibitors, alpha or beta-blockers, angiotensin receptor II blockers, and calcium channel blockers).

We used alternative definitions of hypertension to evaluate the potential misclassification of cases in sensitivity analyses: 1) considering the antihypertensive-like treatment of the medication list in the hypertension definition instead of the self-reported question above, and 2) excluding participants with BP levels close to the cut-off value for hypertension (i.e. we excluded non-medicated participants with SBP and DBP ≥ 135/85 mmHg and < 150/95 mmHg). Besides, we defined "hypertension or prehypertension" which included both hypertensives and prehypertensives as cases. Prehypertensives are commonly classified as non-hypertensive and

are not medicated but have non-optimal BP levels (i.e., SBP or DBP ≥ 120/80 mmHg but below the cut-off for hypertension) (Chobanian et al. 2003) that could be influenced by air pollution.

Exposure assessment

We geocoded participants' residential addresses at enrollment. We estimated annual average outdoor NO_2 ($\mu g/m^3$) at the residences with a city-specific land-use regression (LUR) model (R^2 = 0.63) based on a dense network of residential outdoor NO_2 measurements (years 2007-2009), as described elsewhere (Rivera et al. 2013). The main predictor variables were the height of the sampler and traffic-related variables at different radius buffers (from 25 to 1000 m) around the sampling locations.

To control for acute effects of short-term air pollution and temperature on measured BP, we obtained daily means of temperature and of NO_2 concentrations at an urban background station from the regional air quality monitoring network. Season was categorized as winter (January-March), spring (April-June), summer (July-September), and autumn (October-December).

We also derived long-term average traffic noise levels (dB(A)) 2 m from the façades and at the floors' height of each dwelling with a detailed and validated city-specific noise model (year 2005). This model complies with the European Noise Directive 2002/49/EC (END) and uses the interim European method NMPB routes-96 (CERTU/CSTB/LCPC/SETRA 1997). Estimates were computed at each receptor point by numerical calculations using CadnaA software. The main input variables were: street slopes, type of asphalt, urban topography, and traffic density. Since railway noise has also been associated with BP (Dratva et al. 2012), and a single North-South rail bridge crosses dense traffic areas in the city, we also derived residential railway

noise estimates from an END-based model based on ISO 96/13. The propagation model was built upon source identification of railway noise. This consisted of day-time and nighttime noise measurements of frequencies (in 1/3 octave bands) and equivalent levels (in dB(A)) of freight and normal trains (a total of 72 measurements). Measurements were taken with a SC-30 sound level meter and CB-5 calibrator (CESVA, inc.). As it is suggested that transportation noise may particularly impact cardiovascular health during the restorative sleep processes at nighttime (Jarup et al. 2008), we used the nighttime (11pm-7am) noise indicators (L_{night}). The small airport located outside the city did not affect our study population.

Traffic markers (traffic intensity at the nearest road and traffic load within a 500 m buffer) were collected using the city road network with linked traffic intensities from local registries and traffic (Rivera et al. 2012).

Statistical analyses

We excluded participants with missing information (n = 101) on the outcomes, exposure, or main model covariates. We assessed bivariate associations with Spearman rank correlation between continuous variables, with χ^2 test between categorical variables, and with Kruskal-Wallis test between continuous and categorical variables. We used multivariate linear regression models for BP, logistic regression for hypertension, and performed regression diagnostics. The shape of the association between NO_2 and the outcomes was depicted using smooth splines with multivariate generalized additive models. Inclusion of covariates was based on the hypothesized causal pathway of long-term effects of NO_2 on BP and current evidence (Fuks et al. 2011). We also built saturated models with all covariates univariately associated with the outcome and exposure (p-values < 0.2) and performed backward regression, manually removing the variables

with the highest p-value one-by-one until estimates changed ≥ 20%. If changes were smaller, we stopped when all p-values were < 0.1. Finally, we assessed the inclusion of potential intermediate variables, co-morbidities, and use of different lags for daily temperature and NO_2 levels prior to examination (lags: 1, 2, 3 and the average from 0 to 3 days), compared to lag 0 (used by default). Temporal trend (day of examination) was also examined to control for potential decreasing trends in BP levels over the study period due to improved BP management. As the different model specifications gave similar results (data not shown), we present final estimates with the most parsimonious model based on background regression (i.e., a model with the minimum set of covariates providing the same point estimates as more complex models), to avoid overadjustment and variance inflation. The models were adjusted for the following variables: age, age squared, sex, living alone, educational level, diabetes, BMI, nighttime railway noise, road traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 (lag 0) and temperature (lag 0). We categorized BMI and introduced a square term for age to meet linearity with the outcomes. Non-linearity was assessed a priori with univariate generalized additive models, checking splines, and was later tested in regression diagnostics.

A main objective of this study was to rigorously investigate potential biases related to different methodologies used or proposed to control for BP-lowering medication. Thus, we estimated the effects of NO_2 on BP: a) restricting analysis to participants not taking any BP-lowering medication i.e. in "non-medicated"; b) restricting analysis to "medicated" participants; c) ignoring treatment; d) adjusting for treatment; e) adding a fixed value of mmHg for SBP (+10, 15 and 20) and DBP (+5, 10, 15) to those treated; f) using censored normal regression. This method models the untreated BP levels assuming they are normally distributed. In the medicated

participants, the untreated BP levels are not observed, but they are assumed to be at least as high as the measured levels (right censoring). The model effectively assumes that, given the covariates, untreated BP levels above a certain value have the same distribution in medicated and non-medicated participants. Methodologies from a) to d) were used for comparison with previous literature. Methodologies e) and f) were favored in a comprehensive simulation study, but rely on non-measurable assumptions that might be violated in our study population (Tobin et al. 2005).

We assessed effect modification of the association between NO_2 and BP among non-medicated participants by levels of traffic noise at night [$L_{night} < 55dB(A)$ versus $\geq 55dB(A)$], traffic intensity at the nearest road and traffic load within 500 m as binary variables categorized at the median. We also evaluated age, sex, educational level, smoking, Mediterranean diet, living alone (a marker of uncontrolled hypertension (Morgado et al. 2010), diabetes, CVD, and season of examination (given possibly larger effects in summer (Fuks et al. 2011; Sørensen et al. 2012). Effect modification was tested by adjusting for an interaction term (i.e. NO_2*evaluated categorical variable) and checking its statistical significance (i.e., p-value of interaction) as well as the studied association per categories of the tested variable. The non-medicated group was of primary interest, as the outcome is not influenced by BP-lowering medication in these participants. For comparison purposes, we further evaluated these interactions in the entire sample, using methods e) (adding 10-15 mmHg for SBP and 5-10 mmHg for DBP to measured values) and f) (censored regression) to control for medication. Finally, we tested whether associations for non-medicated and medicated were statistically different by introducing an

interaction term (BP-lowering medication*NO_2) in the model using method d) (adjusting for treatment).

We also performed sensitivity analyses for residential mobility by restricting analyses to subjects not moving in the last 2, 5 and 10 years and checked the time window of exposure by using the average NO_2 exposure of the last 10 years for a subset of 2402 individuals with information on residential history.

Estimated effects on BP and hypertension are expressed per 10-$\mu g/m^3$ increase in NO_2 unless differently specified. We defined statistical significance at an alpha level of 0.05.

Analyses were done using Stata 12.0 (StataCorp, College Station, TX) and R 2.12.

Results

The final sample size consisted of 3,700 individuals. Participants excluded from the study had slightly higher SBP levels, less healthy life-style, more co-morbidities, and lower transportation (i.e. traffic and railway) L_{night} levels (data not shown).

The characteristics of the study population included in the final models are summarized in Table 1 and in the Supplemental Material, Table S1. A 72.6% of all participants did not take any BP-lowering medication (i.e. non-medicated group). Non-medicated differed from medicated participants in being younger on average (53 vs. 68 years old, respectively) but with similar age ranges (35-83 versus 35-82, respectively), having lower BP, higher educational level, less co-morbidities, including a greater proportion of women, and smoking and drinking more.

Home outdoor levels of annual average NO_2, long-term railway L_{night}, and traffic intensity at the nearest road were similar in non-medicated and medicated. The median levels in non-medicated were 26.4 μg/m^3, 41.4 dB(A), and 1400 vehicles/day, respectively. Non-medicated participants had slightly lower traffic L_{night} levels compared to medicated participants (56.5 dB(A) versus 56.9 dB(A), respectively).

The highest correlations of annual mean NO_2 concentrations were with traffic L_{night} (r = 0.74) and traffic load within a 500 m buffer (r = 0.91) (see Supplemental Material, Table S2).

A 10-μg/m^3 increase in annual average NO_2 (from now onwards, NO_2) was associated with a statistically significant increase of 1.15 mmHg (95% CI: 0.34, 1.95) in SBP in non-medicated in univariate analysis (data not shown) and of 1.34 mmHg (95% CI: 0.14, 2.55) after full adjustment (Table 2). This association was less precise in the group of medicated participants (β = 1.19, 95% CI: -1.37, 3.75). The association between NO_2 and SBP in the entire population (with and without adjustment for BP-lowering treatment) yielded similar results (β = 1.11, 95% CI: -0.03, 2.24 and β = 1.35, 95% CI: 0.23, 2.47, respectively). Models adding a fixed value of SBP to medicated participants showed smaller estimated effects, steadily shrinking toward the null with increasing fixed values. No association between NO_2 and SBP was observed with censored regression. The main confounders (i.e., covariates producing the greatest change in point estimates) of the association between NO_2 and SBP were age, transportation noise (both traffic and railway), and daily temperature. Not adjusting neither for traffic and railway noise resulted in a smaller coefficient for NO_2 (β = 0.59, 95% CI: -0.15, 1.34) (Table 2). As additional information, the associations of noise with SBP per 10-dB(A) change in L_{night} in the model for non-medicated participants were β = -0.94 (95% CI: -2.53, 0.64), p-value = 0.244 (traffic noise)

and β = -0.21 (95% CI: -0.63, 0.21), p-value = 0.326 (railway noise) (data not shown). The addition of heart rate, CVD, hyperlipidemia, Mediterranean diet, exercise, day of examination, daily temperature, or daily NO_2 levels at lags different than 0, did not affect results (data not shown). The association between NO_2 and SBP suggested a positive linear trend above 20 $\mu g/m^3$ (see Supplemental Material, Figure S1). We identified no associations of NO_2 with DBP (β = 0.15, 95% CI: -0.57, 0.88) or hypertension (OR = 0.93, 95% CI: 0.79, 1.1) (see Supplemental Material, Tables S3 and S4).

Figure 1 shows the interaction analyses for the association between NO_2 and SBP and DBP, respectively, in non-medicated participants. NO_2 was more strongly associated with SBP among individuals with CVD (β = 5.96, 95% CI: 1.85, 10.08) than among individuals without (β = 1.17, 95% CI: -0.04, 2.38), p-value of interaction = 0.02. With DBP there was evidence of an association only among individuals with CVD (β = 2.71, 95% CI: 0.23, 5.18), p-value of interaction = 0.03). A stronger association between NO_2 and SBP was also found in those living alone (β = 3.93, 95% CI: 1.32, 6.55) compared to those living with more people (β = 1.10, 95% CI: 0.23, 5.18), p-value of interaction = 0.03. NO_2 was associated with SBP in participants exposed to higher traffic levels, particularly to traffic loads above the median within 500 m buffer (β = 2.28, 95% CI: 0.58, 3.97) and not in those exposed to lower levels (β = -0.79, 95% CI: -2.73, 1.15), p-value of interaction=0.007. This was also the case for individuals exposed to traffic $L_{night} \geq 55$ dB(A) (β=1.82, 95%CI: 0.56, 3.07) compared to those exposed to lower noise levels (β=-0.39, 95%CI: -2.17, 1.39), (p-values of interaction=0.03).Associations of NO_2 with SBP and DBP were stronger among participants whose BP was measured in summer versus other seasons, and this seasonal interaction was statistically significant for DBP only (p-value of

interaction = 0.04). Gender, educational level, and diabetes (Figure 1), and age, smoking, and Mediterranean diet (data not shown) did not modify the main associations. Interaction analyses showed the same patterns when a fixed value of mmHg was added to the measured BP levels of medicated subjects, or when censored regression was used to control for medication use (data not shown). Finally, there was no statistical evidence of differences in the observed associations by BP-lowering medication groups (Table 2 and Supplemental Material, Table S3) neither with SBP nor with DBP (p-value of interaction = 0.472 and 0.318, respectively; results not shown).

In a sub-sample with residential history, restricting the sample to non-movers or using 10-year average NO_2 levels yielded similar or slightly smaller increases in BP in non-medicated participants compared to findings with the annual average NO_2 levels at the current address (see Supplemental Material, Table S5).

Discussion

This is one of the only studies to analyze the association between near-road traffic-related air pollution and both blood pressure (BP) and hypertension, and to control for detailed transportation noise information. Moreover, this study evaluates in detail the influence on findings of using different methodologies to control for BP-lowering medication.

This cross-sectional population-based study showed a statistically significant association between long-term exposure to home outdoor nitrogen dioxide (NO_2), a widely used marker of near-road traffic-related air pollution, and systolic blood pressure (SBP) among participants not taking BP-lowering medication (non-medicated). This association was similar in the entire population either adjusting or not for medication, though the latter was slightly weaker. When

using methods proposed to better account for medication in the entire sample, namely methods e) fixed addition and f) censored regression, the relationship was weaker or diluted (Tobin et al. 2005). Associations were adjusted for exposure to transportation noise, short-term air pollution levels, and temperature, and were robust to the inclusion of several covariates (data not shown). No significant associations were generally found for hypertension or diastolic blood pressure (DBP), although we observed associations with DBP in some subgroups of the population.

Blood pressure

The main results for SBP are consistent with most of the few studies available. Fuks et al. (2011) and Schwartz et al. (2012) reported estimated effects with urban background particulate matter of an aerodynamic diameter ≤ 2.5 $\mu g/m^3$ ($PM_{2.5}$) and black carbon, respectively, but they did not analyze NO_2. Regarding NO_2, one study reported inverse associations between nitrogen oxides (NO_x, NO and NO_2) and SBP (Sørensen et al. 2012), a study in China reported no association (Dong et al. 2013), and a survey of elderly in Taiwan (Chuang et al. 2011) reported stronger estimated effects than ours, namely a 11.22 mmHg increase in SBP (95% CI: 8.56, 13.89) per 10-$\mu g/m^3$. Differences among studies may reflect different population characteristics (age, ethnicity, life-style, etc.) or residual confounding. Moreover, to the extent that NO_2 may serve as a marker, differences in the air pollution mixtures between the study areas may also explain the discrepancies.

As reported in two previous epidemiological studies, there was no association between NO_2 and DBP (Auchincloss et al. 2008; Sørensen et al. 2012). Animal and human experimental studies suggest that BP responses to long-term exposure to air pollution may be mediated by sustained systemic inflammation and/or oxidative stress, impairing endothelial function and increasing BP

(Brook et al. 2009; Mills et al. 2008). As discussed by Auchincloss et al. (2008), endothelial dysfunction and subsequent stiffening of the aorta would result in increased SBP but lower DBP, i.e. increased pulse pressure, and subsequent isolated systolic hypertension after age 60 (Franklin 2006).

Effect of BP-lowering treatment

One of the difficulties in studying BP is that antihypertensive medication is a potential mediator between air pollution and measured BP levels, and not a confounder of the studied association. Consequently, the common procedures of adjustment for medication may introduce bias. Previous studies either analyzed non-medicated participants (Sørensen et al. 2012), did not adjust for medication (Chuang et al. 2011), adjusted for medication (Schwartz et al. 2012), or compared models with an without adjustment (Fuks et al. 2011). To overcome this problem, some methodologies have been proposed (Tobin et al. 2005). However, as discussed below, the latter also rely on non-measurable assumptions that may be violated in some populations.

In the non-medicated group, we observed a statistically significant positive association between NO_2 and SBP, whereas no association was observed between NO_2 and BP in medicated participants. These results may agree with the hypothesis that effects of air pollution on BP can be masked by medication, and that the association might be more clearly observed in the non-medicated group. It should though be acknowledged that conditioning on medication can lead to collider stratification bias if air pollution is associated with medication and there is another factor which is associated to both medication and measured BP. NO_2 levels were similar in medicated and non-medicated in the entire population (Table 1) and among hypertensive participants, a fact that may minimize the potential for this bias. The main predictors of being

non-medicated but with hypertension were being younger and healthier, while NO_2 was not associated. However, younger age, which was associated with lower BP levels, also was associated with lower NO_2 levels (Spearman rank $r = 0.11$, p-value < 0.001). While our multivariate models took all these factors into account, one should be aware that residual bias mediated through age or due to unmeasured characteristics cannot be excluded.

As suggested by Fuks et al. 2011, if air pollution leads to high BP, medication intake, and subsequent decreases in measured BP levels, and if this is the only mechanism in place, then we should observe an inverse association between air pollution and measured BP levels. However, given the wide range of the population studied, different treatments potentially used, and likely diverse compliance with treatment, heterogeneity in the treatment effects is expected. This may lead to not observing an inverse relationship but a positive but underestimated one in medicated participants and in the entire population without adjustment for treatment. Under the assumption of heterogeneity, medication would also be a weaker mediator of the association between NO_2 and BP, thus resulting in less bias when adjusting for medication.

Using a fixed addition of 10 mmHg in SBP for those treated led to weaker although positive but not statistically significant association, whereas larger additions showed a steady shrinkage of results towards the null. As suggested by McClelland et al. 2008, in many scenarios the absolute treatment effect will depend on the underlying BP levels and the target therapeutic values to achieve for BP, thus the simple addition of a fixed value would be inadequate. It is worth noting that the difference in BP levels prior to treatment and during treatment may depend on several characteristics (SES, etc.), or unmeasured factors, that can in turn be associated with exposure. This can also bias the results for the fixed addition method. Regarding censored regression, one

of the assumptions of this model is that the distribution of underlying BP in treated subjects is the same as the distribution of measured BP in untreated subjects, which might be often wrong (Tobin et al. 2005), and not necessarily true in our sample. This methodology can also underestimate or overestimate the truth (McClelland et al. 2008).

In summary, no perfect methodology exists to account for BP-lowering medication, as all approaches rely on assumptions regarding the effect of medication that may vary across scenarios and introduce bias. The heterogeneity in the treatment effect may reduce bias that might be introduced by commonly used procedures to account for the effect of medication use. In light of the non-trivial differences in estimated effects across the various methods, more studies are needed to clarify the complex conceptual challenge we raise in this study.

Hypertension

Prevalence of hypertension was not associated with annual average NO_2 concentrations in our study. The few previous studies found inconsistent results for prevalence of hypertension with different pollutants (Dong et al. 2013; Fuks et al. 2011; Johnson and Parker 2009; Sørensen et al. 2012). Regarding incidence of hypertension, no association was found in Denmark (Sørensen et al. 2012), whereas another study reported an increased risk of hypertension which was statistically significant with long-term NO_2 but not with $PM_{2.5}$ (Coogan et al. 2012).

We hypothesized the differences to be due to misclassification of hypertensive cases, as proposed before (Fuks et al. 2011). However, the different definitions of hypertension yielded all null results (see Supplemental Material, Table S4). Alternatively, the null associations may relate to a loss in statistical power, but also of information, when using the binary variable of hypertension. In fact, we observed a non-significant increased OR when assessing

prehypertension and hypertension together. Prehypertensives are non-medicated individuals with sub-optimal BP levels not reaching the cut-off for hypertension. The assessment of this group, which has increased CV risk (Chobanian et al. 2003), might also be informative for the effects of air pollution. Results considering this non-medicated group agree with results on BP and may explain findings among non-medicated. However, by reclassifying prehypertensive participants we are partially reclassifying by medication use. Thus, as explained for the BP analyses among non-medicated, residual stratification collider bias cannot be excluded.

Transportation noise

Road traffic and railway noise have been associated with high BP (Dratva et al. 2012; van Kempen and Babisch 2012; Sørensen et al. 2011). Therefore, we considered transportation noise as a potential confounder. Although traffic noise and NO_2 were highly correlated (r = 0.74), the negative confounding of transportation noise on the studied association with SBP was not explained by collinearity among these factors (mean variance inflation factor (VIF) for the model = 1.45, VIF for NO_2 = 3.2, individual VIF for road L_{night} = 2.25). We hypothesized that the negative confounding might in part be explained by the use of protections against noise among participants more exposed to noise (e.g. closing windows at night, sleeping in a room facing the backyard, etc.). Thus, the estimates of outdoor noise may not be sufficient to investigate the independent effects of this stressor on BP in our setting. In Girona, people live close to traffic and traffic noise is prevalent. Moreover, complaints about neighborhood noise are generally high in Spain. Thus, participants may more likely use remedies against noise in our study area compared to settings with less local traffic or different urban structures. Protections are expected to impact noise exposure to a greater extent than air pollution, as noise propagation depends on

physical barriers, whereas air pollution distributes more evenly and its infiltration rates are high (Chen and Zhao 2011). Moreover, as noise is subject to annoyance, the protective behavior will more likely correlate with noise than air pollution exposure. We consider better noise exposure assessment a crucial next step to elucidate the role of noise. Thus, we currently develop models to individually estimate traffic-related noise levels indoors at home.

Effect modification

We observed a stronger positive association between $NO_2$and BP in participants with CVD, similarly to Sorensen et al. 2012, who reported this interaction between long-term residential NO_x and DBP. However, given the small numbers in both cases, further studies are needed to investigate this interaction. We also found a stronger association for participants living alone. Living alone was strongly correlated with being older and exposed to slightly higher NO_2 levels in our population, and Morgado et al. (2010) identified it as a predictor of uncontrolled hypertension among hypertensives (Morgado et al. 2010).

The association between NO_2 and SBP was stronger in those more exposed to traffic and road traffic noise [≥ 55dB(A)]. This may be due to a non-linearity in the estimated effects of NO_2 on BP. Indeed, we observed a null to negative association at very low NO_2 levels (compared to levels in larger Spanish and European cities) and a clear positive trend from 20 $\mu g/m^3$ onwards (Supplemental Material, Figure S1). Our results did not change by the use of a quadratic term (data not shown), as the non-linearity was observed at very low levels and our sample was distributed across a wider range of NO_2 concentrations. However, the observation of a non-linearity may suggest that, at higher traffic levels, NO_2 may be more representative of near-road traffic related pollutants, being the later particularly associated with CVD

(Auchincloss et al. 2008; Brook et al. 2009; Hoffmann et al. 2007; Künzli et al. 2010). In our study areas, low levels of NO_2 reflect sites with little traffic, thus, exposure is mostly related to urban background pollution whereas, in other urban areas, NO_2 is clearly a marker for near-road traffic-related pollutants. Similar reasons may explain the negative associations observed between SBP and NO_x in Denmark (Sørensen et al. 2012), where many individuals were exposed to particularly low NO_2 levels (median, 5%-95% percentile: 16.3, 12.0 - 32.6, at baseline) compared to those in our study area (26.6, 12.6 - 39.6). In addition, the association between NO_2 and SBP tended to the null when adjusting for traffic intensity or traffic load within 500 m (results not shown), which also suggests that we are observing associations for traffic-related air pollution, rather than for background pollution.

Strengths and limitations

The main inferential limitation of this study was its cross-sectional design. Our results should be confirmed in longitudinal analysis with repeated measures of BP and incidence of hypertension.

As in many epidemiological studies, BP was measured with standard protocols, consisting in repeated measures taken during one single exam, not following clinical procedures to diagnose hypertension. Although results were robust to the different definitions of hypertension and we selected the last BP measurement available to minimize the "white-coat" effect, a residual misclassification of the outcome cannot be excluded. As random error in BP measures can be expected, the misclassification could likely be non-differential, biasing results towards the null.

Regarding exposure misclassification, we assessed individual residential outdoor exposure, not personal exposure. Although people spend a relevant part of their time at home, as observed in different European areas and climates (Schweizer et al. 2007), we cannot conclude whether

time-activity patterns in our population would affect our findings Although our LUR model was developed after the study examinations were completed, LUR models are good predictors of spatial gradients over time (Eeftens et al. 2011). Moreover, no major changes in traffic or monitored background NO_2 levels occurred from 2003 to 2009 (data not shown). Finally we explored whether past exposure influenced the studied associations with BP levels in a sub-sample with residential history. Although the sub-sample was not fully representative of the study population (slightly younger group with lower BP levels), results in this sub-sample were not affected by past residential mobility or by using a longer time window of exposure.

Another limitation was the lack of information on lead exposure from leaded gasoline used before year 2000 in Spain. Long-term cumulative exposure, reflected by bone lead levels, could remain high in this adult population and potentially interact with or confound the association between NO_2 and high BP (Schwartz et al. 2011).

As an important strength, we evaluated a population-based cohort, thus results in the entire population can be generalized, and a wider age range compared to previous studies, some of which were only in elderly participants (Chuang et al. 2011; Schwartz et al. 2012). Additional strengths include the comprehensive analysis of BP-lowering medication, the use of a LUR model that captured the intraurban variability in NO_2 levels and that allowed individual exposure assessment, and the control for many covariates, including detailed transportation noise data, which has rarely been taken into account in previous literature (Fuks et al. 2011; Sørensen et al. 2012).

Conclusions

We observed a positive association between long-term exposure to NO_2 and SBP in a population-based cohort in Girona, after adjustment for transportation noise. The association was sensitive to the selected methodology to control for BP-lowering medication, and was stronger among participants with CVD, those living alone, and those exposed to more traffic and road traffic noise. These results suggest specific effects of near-road traffic-related pollutants on BP. High BP might be a pathway through which air pollution causes CVD. Although the estimated effect size was small, these findings are relevant for public health, given the ubiquity of air pollution, affecting millions of people. Indeed, a "small" reduction of 2 mmHg in the population mean SBP has been estimated to result in a 25% reduction in stroke events (Girerd and Giral 2004).

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Table 1. Main characteristics of the study population (N = 3700) with and without stratification by use of blood pressure (BP)-lowering medication.

Variable	Total (N = 3700)	No medication (N = 2685)	Used medication (N = 1015)	p-Value[a]
Continuous variables [median (IQR)]				
Systolic blood pressure (mmHg)	125 (26.0)	120 (22.0)	139 (27.0)	< 0.001
Diastolic blood pressure (mmHg)	78.0 (13.0)	77.0 (12.0)	81.0 (14.0)	< 0.001
Age (years)	57.0 (20.0)	53.0 (17.0)	68.0 (15.0)	< 0.001
Deprivation index[b]	-1.82 (1.28)	-1.82 (1.22)	-1.81 (1.37)	< 0.001
Annual average NO_2 levels ($\mu g/m^3$)	26.6 (11.7)	26.4 (11.6)	26.8 (11.9)	0.837
Traffic L_{night} (dB(A)), 11pm-7am	56.6 (7.00)	56.5 (7.00)	56.9 (7.10)	0.022
Railway L_{night} (dB(A)), 11pm-7am	41.2 (15.2)	41.4 (15.0)	41.0 (15.2)	0.056
Daily mean NO_2 levels, lag 0 ($\mu g/m^3$)	32.0 (11.9)	32.0 (11.7)	31.7 (12.6)	0.362
Daily mean temperature, lag 0 (ºC)	14.5 (12.4)	14.3 (12.8)	15.0 (11.7)	0.021
Categorical variables [N (%)]				
Hypertension, yes	1478 (39.9)	565 (21.0)	913 (90.0)	< 0.001
Gender, male	1720 (46.5)	1203 (44.8)	517 (50.9)	0.001
Body mass index, < 20	135 (3.60)	124 (4.60)	11 (1.10)	< 0.001
0-25	1110 (30.0)	939 (35.0)	171 (16.8)	
25.1-30	1618 (43.7)	1168 (43.5)	450 (44.3)	
> 30	837 (22.6)	454 (16.9)	383 (37.7)	
Living alone, yes	413 (11.2)	265 (9.90)	148 (14.6)	< 0.001
Educational level, university or similar	1050 (28.4)	853 (31.8)	197 (19.4)	< 0.001
Secondary	1110 (30.0)	878 (32.7)	232 (22.9)	
Primary	1432 (38.7)	902 (33.6)	530 (52.2)	
Illiterate	108 (2.90)	52 (1.90)	56 (5.50)	
Smoking, never smokers	1881 (50.8)	1329 (49.5)	552 (54.4)	< 0.001
Smokers	811 (21.9)	677 (25.2)	134 (13.2)	
Former smokers	1008 (27.2)	679 (25.3)	329 (32.4)	
Diabetes, yes	580 (15.7)	265 (9.90)	315 (31.0)	< 0.001

Variable	Total (N = 3700)	No medication (N = 2685)	Used medication (N = 1015)	p-Value[a]
Daily alcohol intake (g/l), no alcohol	956 (25.8)	630 (23.5)	326 (32.1)	< 0.001
Little (< 20)	2237 (60.5)	1672 (62.3)	565 (55.7)	
Moderate (20.1-39.9)	390 (10.5)	292 (10.9)	98 (9.70)	
Excessive (≥ 40)	117 (3.20)	91 (3.40)	26 (2.60)	
Cardiovascular disease[c,d], yes	269 (7.30)	83 (3.10)	186 (18.5)	< 0.001

NO_2: nitrogen dioxide; L_{night}: long-term average nighttime noise levels.

[a]χ^2 test and Kruskal-Wallis test for strata of BP-lowering drugs with categorical variables or continuous variables, respectively. [b]High deprivation corresponds to high values. [c]Myocardial infarction, ictus, or any cardiovascular surgical intervention. [d]N below 3700 (< 1% missing observations).

Table 2. Estimated effect of a 10-μg/m^3 increase in annual average home outdoor NO_2 concentrations and 95% confidence intervals on systolic blood pressure (SBP, mmHg).

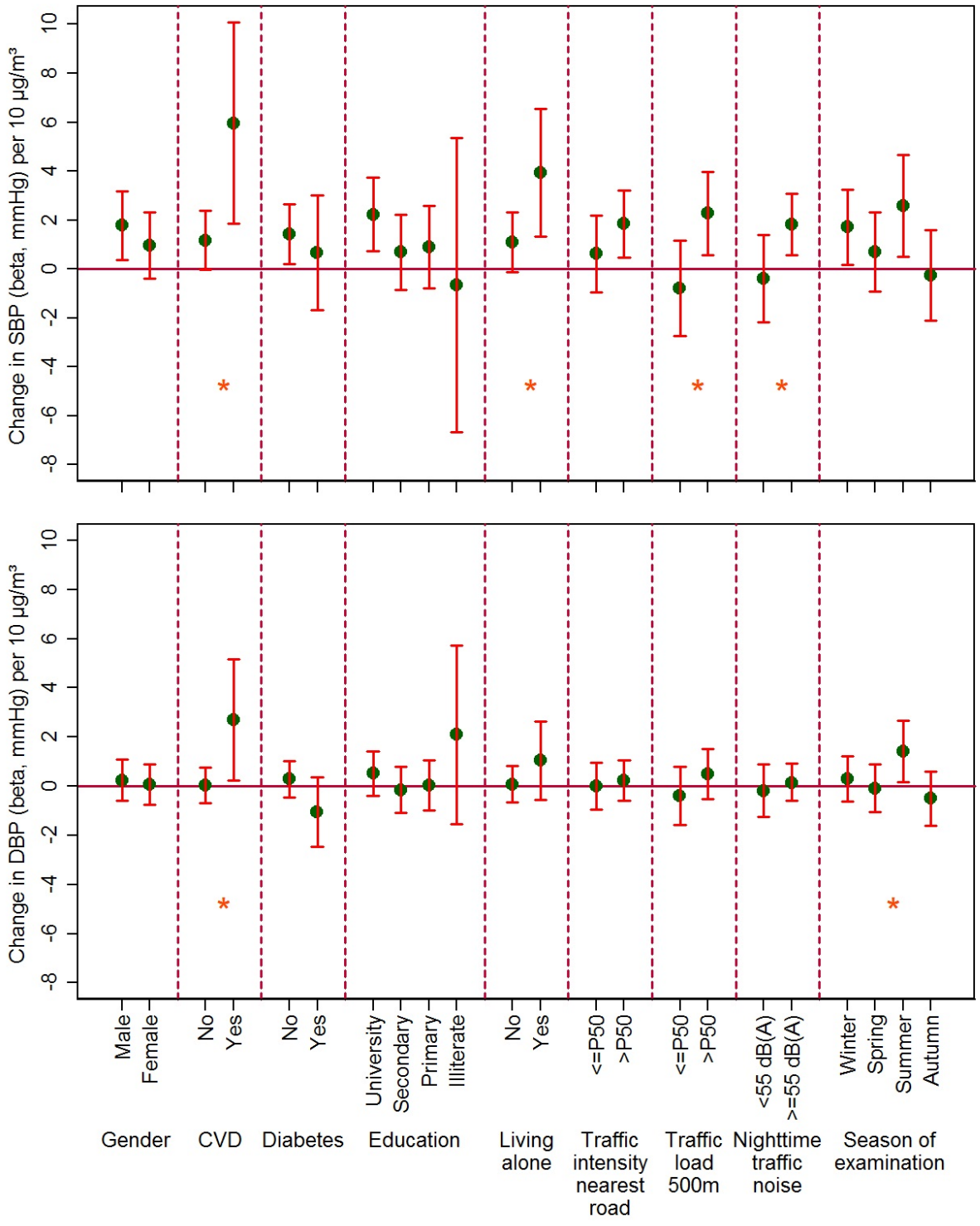
Models for SBP	**N**	**beta (95% CI)[a]**	**beta (95% CI)[b]**
Non-medicated	2685	1.34 (0.14, 2.55)	0.59 (-0.15, 1.34)
Medicated	1015	1.19 (-1.37, 3.75)	0.68 (-1.09, 2.44)
Without adjustment for medication	3700	1.11 (-0.03, 2.24)	0.56 (-0.17, 1.28)
With adjustment for medication	3700	1.35 (0.23, 2.47)	0.67 (-0.04, 1.38)
+10 mmHg[c]	3700	0.78 (-0.43, 2.00)	0.41 (-0.36, 1.18)
+15 mmHg[c]	3700	0.62 (-0.65, 1.89)	0.33 (-0.47, 1.14)
+20 mmHg[c]	3700	0.46 (-0.88, 1.80)	0.26 (-0.59, 1.11)
Censored regression	3700	0.38 (-0.98, 1.73)	0.12 (-0.73, 0.97)

[a]Multivariate linear regression models, adjusted for: age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0). [b]Models adjusted for covariates in [a] except for nighttime railway and traffic noise. [a] and [b] adjusted for BP-lowering medication if specified in table. [c]Addition to SBP for participants with BP-lowering medications.

Figure Legend

Figure 1. Adjusted beta coefficients and 95% confidence intervals for the association of systolic (SBP) and diastolic (DBP, mmHg) blood pressure with a 10-$\mu g/m^3$ increase in annual average home outdoor NO_2 concentrations by subgroups of the population (N = 2685, non-medicated participants). Each multivariate linear regression model was adjusted for the corresponding interaction term, one at a time, and age, age squared, sex, living alone, education, diabetes, BMI, nighttime railway noise, nighttime traffic noise, smoking, alcohol consumption, deprivation, daily NO_2 and temperature (lag 0). *indicates p-value of interaction < 0.05.

Figure 1.


Change in SBP (beta, mmHg) per 10 µg/m³
Change in DBP (beta, mmHg) per 10 µg/m³
-8
-6
-4
-2
0
2
4
6
8
10
*
Male
Female
No
Yes
No
Yes
University
Secondary
Primary
Illiterate
No
Yes
<=P50
>P50
<=P50
>P50
<55 dB(A)
>=55 dB(A)
Winter
Spring
Summer
Autumn
Gender
CVD
Diabetes
Education
Living alone
Traffic intensity nearest road
Traffic load 500m
Nighttime traffic noise
Season of examination